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Title

Management of polymyalgia rheumatic in older people

Short running title

Management of polymyalgia rheumatica

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Management of polymyalgia rheumatica

Abstract

Polymyalgia rheumatica (PMR) is the most common inflammatory rheumatic disease affecting older people. For decades it has remained under-researched and poorly understood despite causing significant disability. Once thought to be a self-limiting condition universally responsive to a limited course of prednisolone, it is now clear that most people with PMR require prolonged corticosteroids beyond two years. The cumulative burden of adverse effects from such therapy is thought to substantively contribute to reduced functionality and frailty in older patients, yet few effective alternative pharmacotherapies have been established. This review explores the latest developments regarding the impact of conventional corticosteroid treatment in PMR and the emerging potential of steroid-sparing agents.

Introduction

Polymyalgia rheumatica (PMR) is an inflammatory autoimmune disease occurring almost exclusively in individuals older than 50 years of age and predominantly affecting structures

of the shoulder and hip girdle. First described as 'senile rheumatic gout' in 1888, the term 'polymyalgia rheumatica' was coined in 1957 in reference to the diffuse and inflammatory nature of the pain experienced by sufferers.[1,2] The aetiology of PMR remains unclear, although genetic factors appear to contribute, and infectious precipitants have been proposed due to the observation of seasonal peaks in diagnosis.[3] Women are up to two times more likely to be affected than men, with the lifetime risk of PMR estimated to be 2.4% in women and 1.7% in men, ranking second only to rheumatoid arthritis amongst inflammatory rheumatic conditions.[4] The incidence rate of PMR increases steadily with advancing age resulting in a mean age at diagnosis of 70-73 years old.[5]

Clinical Presentation and Diagnosis

The hallmark presenting symptoms of PMR are pain and stiffness involving the shoulder and hip girdle, with symptoms commonly also described in the neck, lower back and thighs. Involvement of hands and wrists is possible, occasionally manifesting as remitting seronegative symmetrical synovitis with pitting oedema (RS3PE) characterised by diffuse and marked pitting oedema of the entire hand, usually bilaterally.[6] Symptoms of PMR are classically at their peak in the morning, with patients often reporting significant difficulty rising from bed or getting dressed. True weakness is not typical but may be described by patients in relation to their impaired mobility resulting from pain and stiffness. Constitutional symptoms including fever, fatigue and unintentional loss of weight can also occur.

Classification criteria for PMR exist (Box 1) but are primarily intended to define a homogenous population in research settings rather than as diagnostic criteria in clinical practice. In practice, not all patients with PMR will fulfil these criteria, thus PMR remains a clinical diagnosis based on a construct of typical symptoms together with raised inflammatory markers, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). ESR is classically highly elevated in PMR, but cases do occur with normal levels.[7] There are no gold standard diagnostic tests for PMR, although imaging modalities including ultrasound, magnetic resonance imaging (MRI) and ^{18}fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) can show supportive findings.

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Box 1. 2012 European League Against Rheumatism (EULAR) / American College of Rheumatology (ACR) Classification Criteria for Polymyalgia Rheumatica[8]	
Required criteria: • Age ≥ 50 years • Bilateral shoulder pain • Abnormal erythrocyte sedimentation rate (ESR) and/or C-reactive protein (CRP) PLUS, a score of ≥ 4 (or ≥ 5 if ultrasound criteria is used) from the following:	
Clinical Criteria	
• Morning stiffness lasting >45 minutes	2 points
• Hip pain or restricted range of motion	1 point
• Negative rheumatoid factor and anti-citrullinated protein antibody	2 points
• Absence of other joint involvement	1 point
Ultrasound Criteria	
• ≥ 1 shoulder with subdeltoid bursitis, biceps tenosynovitis, or glenohumeral synovitis AND ≥ 1 hip with synovitis or trochanteric bursitis	1 point
• Both shoulders with subdeltoid bursitis, biceps tenosynovitis, or glenohumeral synovitis	1 point

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97 In the absence of specific tests for PMR, differential diagnoses should always be actively
98 considered particularly given the propensity for a broad range of conditions to present with
99 an initial polymyalgic onset (Box 2).

100

Box 2. Differential diagnoses of PMR to consider
Inflammatory rheumatic diseases

- Late-onset rheumatoid arthritis
- Late-onset spondyloarthritis
- Connective tissue diseases (e.g. vasculitis)
- Calcium pyrophosphate deposition disease

Non-inflammatory rheumatic diseases

- Rotator cuff pathology
- Shoulder osteoarthritis
- Adhesive capsulitis
- Fibromyalgia

Other

- Viral or bacterial infections
- Malignancy
- Parkinson's disease

Approximately 20% of patients with PMR will develop an associated condition, giant cell arteritis (GCA), at some time during their lives.[3] Correspondingly, around 50% of patients with GCA will be affected by PMR symptoms either preceding or concurrent with their GCA presentation, or alternatively manifesting during disease relapses.[3] GCA is a vasculitis affecting medium to large arteries, with classic presenting symptoms including severe headache, scalp tenderness, jaw claudication and visual symptoms. If left untreated GCA can result in permanent visual loss, therefore clinicians should actively enquire about symptoms suggestive of GCA in patients with PMR, the presence of which should prompt urgent rheumatological review followed by escalation of corticosteroids to 40-60mg prednisolone equivalent if clinical suspicion is high.

Long-Term Corticosteroid Monotherapy Remains the Standard of Care in PMR

Shortly after their development for medical use in the late 1950s, corticosteroids became the cornerstone of therapy in PMR. Treatment strategies have not evolved since then, making PMR one of the few conditions where current-day standard of care still dictates

long-term corticosteroid monotherapy, generating significant implications for a geriatric population susceptible to corticosteroid toxicity.

Prednisolone is typically commenced at a low to moderate dose and tapered gradually until cessation, whilst monitoring for disease recurrence. However, the ideal starting dose and reduction rate is unclear. As is the case in many rheumatic conditions, current recommendations for prednisolone dosing in PMR are largely based on collective clinical experience due to the paucity of high-level evidence from which to draw upon.

The available evidence would suggest that an initial dose of prednisolone less than 10mg is likely insufficient to control symptoms, whilst a small increase to even 12.5mg may be adequate for most patients.[9,10] A slow weaning plan that aims to cease prednisolone after more than a year is associated with less relapses of disease than quicker cessation within three or nine months.[11] Excessively rapid reduction of prednisolone can also precipitate symptoms of steroid withdrawal including arthralgias, malaise and fatigue, mimicking symptoms of PMR relapse and confounding the clinical picture. In practice, a starting prednisolone dose of 15mg daily is most commonly used, tapered over roughly 12 to 18 months in line with guidelines published by the British Society for Rheumatology (Box 3).[12]

Box 3. British Society for Rheumatology (BSR) and British Health Professionals in Rheumatology (BHPR) guidelines for the management of polymyalgia rheumatica[12]

- Daily prednisolone 15mg for 3 weeks
- Then 12.5mg for 3 weeks
- Then 10mg for 4-6 weeks
- Then reduction by 1mg every 4-8 weeks

Patients classically have a dramatic response to corticosteroids, sometimes demonstrating improvement within less than 24 hours, although a third of patients will have persistent features of active disease even after three weeks of therapy.[5] Gastroprotection with a proton pump inhibitor should be considered initially (for example, when the prednisolone

dose is greater than 7.5mg daily) or when additional risk factors for gastritis and peptic ulcer disease are present.

Intramuscular injections of methylprednisolone, starting at a dose of 120mg every three weeks have been shown to be as effective as oral prednisolone, with a lower cumulative steroid dose at 96 weeks.[13] This represents an alternative treatment strategy that may be preferable particularly if patient medication compliance is problematic.

Once thought to be a benign and self-limiting condition treatable with a finite course of prednisolone, mounting evidence now points to the need for protracted therapy in many PMR patients. The median duration of corticosteroid treatment for PMR is 1.93 years, with a median cumulative prednisolone dose of 5400mg.[14,15] Up to 60% of patients remain on corticosteroids beyond two years.[16,17] This is predominantly attributable to the frequency of relapses, which occur in 30-50% patients during the first 12-18 months of therapy, usually within two weeks of reducing steroids.[5,18] Relapses necessitate return to the last dose of steroids at which symptoms were controlled, followed by a repeat weaning attempt after one to two months. Patients are typically able to wean prednisolone to a daily dose of approximately 5mg, but commonly have difficulty achieving lower doses without a return of symptoms.[17,19] Concerningly, one in four patients will require greater than four years of corticosteroid therapy.[14] Even after cessation of therapy, disease recurrence is possible as late as 15 years after steroid-free remission is first achieved.[16,17,20]

The concept of two disparate populations within PMR has been proposed – those with self-limiting disease versus those with disease persistence. Clinical features that predict disease trajectory are key to improving management of PMR but remain elusive. Baseline ESR and persistently elevated CRP have shown some promise whilst baseline ultrasound imaging appears to be unhelpful.[18,21,22] PMR therefore remains one of the most common reasons for long-term corticosteroid use.[23]

Corticosteroid-Related Adverse Effects

The long-term corticosteroid use in PMR is inevitably associated with a risk of adverse effects (AEs). Corticosteroid-related complications are well recognised from experience in other conditions and can have even greater implications within the PMR population owing to their older age, consequent higher level of comorbidity, and the compounding effect of the disease itself. Despite only low to moderate doses of prednisolone being used in PMR, up to 65% of patients experience at least one steroid-related AE.[15,16] The true rate is likely higher, as steroid-related AEs are often not actively enquired about or documented in medical records.[16]

In many rheumatic conditions, it is generally accepted that long-term prednisolone doses ≤ 5mg daily may have an acceptably low level of harm to justify their use.[24] It is difficult to know if this holds true for an older PMR population, who conceivably already have reduced muscle and bone mass as well as greater accumulated cardiovascular comorbidity. Advancing age and cumulative corticosteroid dose have been identified as risk factors for steroid-related AEs in PMR patients, suggesting that continuation of even low dose corticosteroids may be increasing the risk of harm in older patients.[15] Furthermore, PMR patients who are able to cease corticosteroids within two years have a significantly lower risk of steroid-related AEs (15.6%) than those who remain dependent beyond two years (79.8%).[25] Contrary findings from a recent population-based study however found no difference between PMR patients and controls in the 5-year cumulative incidence of serious corticosteroid-related AEs, other than cataracts.[19]

Prescribers and pharmacists involved in the care of PMR patients should counsel patients regarding the potential adverse effects of corticosteroid therapy (Box 4). Diabetes, osteoporosis and cardiovascular disease are prioritised by both patients and clinicians as being of greatest concern and are thus discussed here in more detail.[26] Patients additionally rank weight gain, thinning of the skin, easy bruising, sleep disturbance, gastro-oesophageal reflux and muscle weakness as being of high concern.[27]

Box 4. Potential adverse effects of corticosteroid therapy
Cardiovascular

- Hypertension
- Fluid retention
- Dyslipidaemia
- Atrial fibrillation

Endocrine / Metabolic

- Diabetes mellitus
- Increased body weight
- Cushingoid appearance
- Adrenal suppression

Musculoskeletal

- Osteoporosis
- Myopathy

Gastroenterological

- Gastro-oesophageal reflux
- Gastritis
- Peptic ulcer disease

Immunologic

- Infection

Psychiatric

- Sleep disturbance
- Mood disturbance
- Psychosis

Ophthalmic

- Cataracts
- Narrow-angle glaucoma

Skin / soft tissue

- Skin atrophy
- Easy bruising

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203 *Endocrine Effects*

Corticosteroids induce hyperglycaemia through multiple mechanisms, primarily resulting in insulin resistance within hepatic, muscle and fat cells.[28] The consequence is new-onset steroid-induced diabetes (NOSID) or worsened glycaemic control in people with pre-existing diabetes . The rate of *de novo* diagnoses of diabetes in PMR patients has been estimated to be twice as high as would be expected from an age- and gender-matched population without PMR.[15] Similar rates were demonstrated in a study specifically of older patients (all greater than 66 years old; mean age 74.9 years) treated with corticosteroids across indications.[29] Interestingly, traditional risk factors including family history, sex and ethnicity do not appear to affect the risk of NOSID.[28]

Patients with PMR treated with corticosteroids should have regular monitoring of their blood glucose level. Prednisolone is usually administered in the morning, reaches its peak effect after four to eight hours (in the afternoon), and lasts 12-16 hours, thus the ideal time to detect hyperglycaemia is after lunch, while a fasting glucose level measured in the morning may remain relatively normal despite corticosteroid use.[28] HbA1c testing may be performed but since levels reflect average blood glucose over the preceding three months sensitivity for hyperglycaemia is lower in newly diagnosed PMR, when steroid doses are also at their highest. Consistently elevated blood glucose levels or an elevated HbA1c should be managed with diet and exercise modifications as well as the addition of an oral hypoglycaemic agent if necessary. The commencement of insulin is uncommonly required in PMR.

Cardiovascular Effects

Exposure to corticosteroids may result in the development of cardiovascular risk factors including diabetes, hypertension and dyslipidaemia, as well as having a direct effect on increasing cardiovascular risk. However, chronic inflammation is similarly thought to contribute to atherosclerosis. There is conflicting evidence regarding whether or not patients with PMR are at greater risk of vascular events such as myocardial infarction, stroke or peripheral arterial disease. Some studies have suggested an increased risk up to 2.6 times that of a control population,[30,31] whilst others have not supported this finding.[32,33] These discordant results may be a result of the complex interaction between corticosteroids, chronic inflammation and cardiovascular risk. The effect of corticosteroids

on cardiovascular risk in PMR patients may therefore be paradoxical, owing to the suppression of inflammation and its associated cardiovascular risk. This is partially supported by one large population-based study, which showed a trend towards a protective effect of corticosteroids on cardiovascular risk, although this was not statistically significant.[32]

All PMR patients should have regular monitoring of cardiovascular risk factors including blood pressure, fasting lipids and glucose, which should be treated as appropriate.

Musculoskeletal Effects

Patients with PMR are 1.5 – 5 times more likely to sustain a fracture than age- and gender-matched individuals without PMR.[15,34] In part, this relates to an increased risk of corticosteroid-induced osteoporosis, with bone density being significantly reduced at both spine and hip after 12 months of treatment for PMR.[21] The greatest increase in risk relates to vertebral fractures, reflecting the particularly detrimental effect of corticosteroids on trabecular bone.[15,35]

In addition to an increased risk of osteoporosis, the higher rate of fractures may be partly attributable to a higher rate of falls seen in patients with PMR.[34] The mechanisms contributing to this are uncertain but may conceivably be due to decreased mobility owing to PMR itself, as well as corticosteroid-related myopathy. Myopathy occurs in up to 60% of patients exposed to corticosteroids, with a higher risk seen in those who are older and immobile.[36] Patients with PMR are at high risk of developing sarcopenia owing to their older age, impaired mobility and exposure to corticosteroids, but exact rates are unknown.

Corticosteroids increase the excretion of urinary calcium. Therefore, people with PMR should be advised to have an adequate calcium intake (1000mg/day), which can be achieved with supplementation where dietary intake is insufficient.[35] Vitamin D supplementation is recommended in all patients.[35] Bone mineral density should be performed using dual-energy x-ray absorptiometry (DEXA) shortly after the commencement of corticosteroids in PMR and repeated on an annual or biennial basis depending on the patient's age and current corticosteroid dose. Anti-resorptive therapy

(bisphosphonates or denosumab being first-line choices) should be commenced in patients found to have osteoporosis, patients with osteopenia in the context of ongoing corticosteroid therapy, or in those with a history of fragility fracture. Ultimately, corticosteroids should be ceased as soon as possible, with fracture risk decreasing markedly once this is achieved.[35]

The cumulative burden of corticosteroid toxicity in PMR patients is therefore substantial. Corticosteroids should be minimised whenever possible, but not at the expense of disease activity. In the older PMR population, corticosteroids contribute to morbidity and frailty, sometimes necessitating the use of a steroid-sparing agent.

Steroid-Sparing Agents in PMR

Data to support the use of specific steroid-sparing agents in PMR is unfortunately limited, thus their initiation is restricted to situations of recurrent disease relapse or early difficulty weaning corticosteroids (for example, if prednisolone dose remains >10mg daily). Steroid-sparing agents are initiated concurrent with a stable prednisolone dose and weaning of prednisolone is re-attempted after one to two months, allowing time for the steroid-sparing agent to reach maximal effect first.

In older people, the risk of toxicity or potential drug interactions associated with commencing an additional immunosuppressive drug must be weighed carefully against the risk of continuing low-moderate dose prednisolone. The individual's current dose of prednisolone and their comorbidities should be considered. Steroid-sparing agents in PMR should only be commenced under the supervision of a rheumatologist given their potential for toxicity and the close monitoring required.

The most supportive data for steroid-sparing agents in PMR exists for methotrexate, leflunomide and tocilizumab. Other agents such as azathioprine and TNF-inhibitors have been trialled in PMR, but results have suggested poor tolerability or inconsistent efficacy.

Methotrexate

Low-dose methotrexate is used ubiquitously in the treatment of many rheumatic conditions, most notably rheumatoid arthritis where it remains the first-line disease-modifying anti-rheumatic drug. In patients with newly diagnosed PMR, the steroid-sparing effect of methotrexate has been demonstrated in one double-blinded randomised controlled trial, although this effect only became significant after 48 weeks and was clinically modest.[37] The trial used a dose of 10mg weekly but in practice methotrexate doses of up to 25mg weekly are prescribed for patients with PMR.

Common adverse effects of methotrexate include nausea, fatigue, alopecia and headache. More severe adverse effects include mucosal ulcers, increased infection risk, hepatotoxicity, bone marrow suppression and pulmonary fibrosis. Folic acid supplementation (1-5mg per day taken between one to seven days per week) is recommended to minimise the frequency and severity of adverse effects.[38]

Several considerations must be taken into account when commencing methotrexate in older patients. As methotrexate is predominantly renally cleared, it is contraindicated if creatinine clearance is below 10mL/min, and dose reductions are warranted if below 50mL/min.[38] Caution should be exercised in any patient with pre-existing liver disease (including hepatosteatosis) or pulmonary fibrosis, where alternative agents are usually preferred given the toxicity profile of methotrexate. Screening with hepatitis B and C serology and a chest radiograph may be considered if risk factors or symptoms are present.[39] Patients should be carefully counselled about the correct dosing of methotrexate (being once weekly rather than daily), and patients with memory impairment may require strategies to reduce the risk of over-dosing, such as sealed weekly calendar packs. Due to the risk of myelotoxicity, the concurrent use of methotrexate with other folic acid anti-metabolites such as trimethoprim is best avoided,[39] which is particularly pertinent for older women in whom this is a common treatment of urinary tract infection. All patients receiving methotrexate should have regular blood tests (for example, every month for the first three months, then every three months thereafter) to monitor for myelotoxicity and hepatotoxicity.[39]

Whilst the toxicity profile of methotrexate should not be underestimated, it is equally important that prescribers and pharmacists do not incorrectly attribute the risks of high-dose methotrexate (used in solid and haematological malignancies) to low-dose methotrexate. Contrary to common belief, low-dose methotrexate used in rheumatic diseases does not necessitate the same precautions for exposure to the patient's bodily fluids as high doses require, and concurrent use with proton pump inhibitors or non-steroidal anti-inflammatory drugs is not contraindicated.

Leflunomide

Leflunomide is another disease-modifying anti-rheumatic drug commonly used in rheumatoid arthritis. Two case series have supported its efficacy in PMR, and a phase 3 trial is planned.[40,41] Its use in PMR is off label and in practice is reserved for patients who are intolerant or resistant to methotrexate. Furthermore, in cases of renal impairment where methotrexate is contraindicated, leflunomide can be used without dose reduction as it is predominantly hepatically cleared. Leflunomide doses of 10 to 20mg daily are typically used.

Common adverse effects of leflunomide include diarrhoea (dose-dependent), nausea & vomiting, alopecia, reversible asymptomatic elevations of liver enzymes and increased risk of infections.[42] Less commonly, leflunomide can result in severe liver injury, bone marrow suppression, hypertension, peripheral neuropathy and leflunomide-induced lung injury (including interstitial pneumonitis and pulmonary fibrosis). Due to extensive enterohepatic recirculation, the half-life of leflunomide is long; washout with cholestyramine may be necessary in cases of major toxicity.[43] Regular blood tests to monitor for myelotoxicity and hepatotoxicity should be performed in patients receiving leflunomide.

Tocilizumab

Tocilizumab is a humanised monoclonal antibody that inhibits the action of interleukin-6 (IL-6) by binding to IL-6 receptor. The rationale for its use in PMR stems from the central role that IL-6 is thought to play in PMR pathogenesis, as well as the successful use of tocilizumab in giant cell arteritis.[44,45] The efficacy of tocilizumab for controlling symptoms

and providing a steroid-sparing effect in newly diagnosed PMR has been demonstrated in two open-label trials, with Phase 3 trials now underway.[46,47]

Tocilizumab is available in both subcutaneous and intravenous forms, typically used at doses of 162mg weekly and 8mg/kg every four weeks, respectively. At present the use of tocilizumab for patients with PMR is not covered by the Australian Pharmaceutical Benefits Scheme and comes at a considerable cost of approximately A$20,000 per annum.

Possible adverse effects include abnormal liver enzymes (usually asymptomatic and reversible), neutropaenia, hyperlipidaemia, hypertension and increased risk of infection, including reactivation of latent infections. In addition, lower gastrointestinal perforation is slightly more frequent in patients receiving tocilizumab, and may present atypically without severe abdominal pain or raised inflammatory markers.[48] Clinicians should also be aware that physiologic production of CRP is dependent on IL-6, thus patients receiving tocilizumab may have artificially suppressed levels. The presence of a normal or low CRP level should therefore not provide reassurance for the lack of significant infection in a patient receiving tocilizumab.

All patients should have screening for infections such as hepatitis B, C and tuberculosis prior to commencement of tocilizumab. While receiving tocilizumab, regular monitoring of liver function tests, neutrophil counts and lipid profiles is warranted.

Conclusion

PMR is a common inflammatory condition affecting older patients. Treatment has remained unchanged for decades, relying predominantly on corticosteroid monotherapy. Despite the use of low to moderate corticosteroid doses, people with PMR often experience a high cumulative steroid burden and consequent toxicity because they may remain dependent on corticosteroids for years. Corticosteroid-related adverse effects are of even greater detriment to an older population owing to their higher level of comorbidity, thus contributing to frailty and significant functional impairment. Although a clear need for alternative therapies in PMR exists, there remains a lack of evidence to support the routine

use of any specific agent at present. Future therapy will need to focus on minimising the adverse impact of PMR and its treatment on older patients.

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